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A study to determine the value of intravenous administration of sodium stibogluconate (Pentostam) for treatment of mucocutaneous leishmaniasis, involved 16 patients, 9 females and 7 males.

The dose was 20 mg/kg body weight for 28 days. Thirteen patients completed the full course, while in 3 treatment was interrupted due to adverse side effects, such as cardiac alterations, elevation of transaminases, vomiting, arthralgias and myalgias. Of the 13 patients who completed treatment, ten were healed, and no relapses appeared in follow-up periods of 9-15 months. One was completely healed at the end of treatment and the others healed more slowly; they were considered healed after 6-11 months.

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__X__For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

for Rolando Sáenz, M.D., P.I.

12/21/90

PI Signature **Date**

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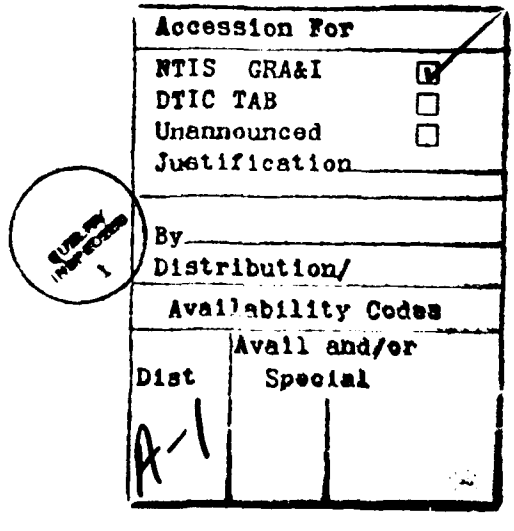

Studies of the therapeutic value of sodium stibogluconate (Pentostam) in the treament of mucocutaneous leishmaniasis (MCL) were continued thru FY '89.

From December 1987 to February 1990, 16 patients with MCL were enrolled in the study. Nine were female and 7 male. The majority (13/16) were between the ages of 18 to 33 years old. They came from rural communities of endemic cutaneous leishmaniasis (CL) in the Provinces of Panama, Colón, Coclé and Chiriquí. Four of the 16 patients had had treatment for leishmaniasis. Ten had no previous treatment, and two did not know if they had any treatment.

In 5/16 patients the mucosal involvement occurred during the primary cutaneous infection, four by direct extension from the lesion on the nose, and one presumably through metastases from an active cutaneous lesion on the leg. In eight patients the mucosal lesion occurred 8 to 58 years after the primary infection. Upon physical examination, 8 of the 16 patients had the characteristic hypopigmented and depressed scars of healed CL. The lack of scars or active lesions in three patients suggests that subclinical or minimal initial CL may also lead to MCL.

The infection was located in the nasal mucosa in all patients and was considered moderate in 10 and mild in 6 (definition: mild, when the infection is localized in the nasal mucosa and is less than 1.5 cm in diameter; moderate,

when there is a perforated septum or a localized lesion in the nasal mucosa of more than 1.5 cm; severe, when there is involvement of more than one anatomical area, nasal, oropharynx, larynx and the presence of extensive destructive lesions).

The nasal septum (15/16), and the inferior turbinate (8/16) were the most common sites for the infection. No extension of the disease beyond the nasal structure was seen (i.e. nasal structures and oral pharynx, oral cavity, larynx, etc.). (Table 1)

Granulomatous lesions were observed in 10/16 patients, ulceration in 5/16 patients, perforation of the septum in 1/16 patients and marked atrophy of the inferior turbinate in 2/16 (Table 2).

Nasal obstruction 16/16, epistaxis 7/16, rhinorrhea 7/16 and itching 6/16 were the most common presenting symptoms (Table 3).

The Montenegro skin test and the serology by indirect immuno fluorescence (IFA) were positive in all patients. The direct smear of biospy material was positive in 8/16, biopsy in 1/5, and isolation of parasites by culture was positive in 4/16. The four isolates were characterized by isoenzyme electrophoresis as Leishmania panamensis.

Hospitalized patients were treated with Pentostam (intravenously), 20 mg per kg of body weight daily for 28

days. Thirteen patients completed the full course of treatment, and in three, treatment was interrupted due to toxicity. The following adverse effects were considered drug associated: arthralgias in 10/16, myalgias 9/16, leucopenia with neutropenia in 5/16 and transient elevation of transaminase in 7/16. ECG abnormalities were detected in 7/16 patients and these include: first degree A-V block in one, premature ventricular contractions in one and changes in ventricular depolarization in five. There was no prolongation of Q-T interval (Table 4). The ECG changes returned to normal after treatment was stopped.

After discharge from the hospital, all 16 patients have been under evaluation in the ENT Clinic of Santo Tomas Hospital, as well as in the GML Clinic.

Three patients did not complete treatment because of toxic reactions. One, a 32 year-old male (WR-13) developed cardiac alterations (premature ventricular contractions and ischemic changes in the left ventricule) after 21 days of therapy at which time treatment was suspended. The patient left the hospital and has not returned.

A second patient, female, 70 years-old (WR-15), developed cardiac alteration after 14 days of therapy. The patient also developed fever, nausea, diarrhea, anorexia, and ECG minimal changes of repolarization. No improvement of the mucosal lesion was observed. Therapy was discontinued and the subsequent follow up at 10 months shows some progression of the infection.

A third patient, female, 32 years-old (WR-11), was treated for 13 days, and developed severe headache, myalgia, artralgia, liver enzyme increase to GOT 126, GPT 120, and neutropenia with a white blood cell decrease to 2,294. At this time there was no improvement in the lesion, and treatment was terminated. At the end of 13 months follow up, parasites were still present.

Thirteen patients received the full course of therapy. Of these, three were considered failures; one (WR-2), a 23 year-old female never showed improvement of the lesion and has remained parasitologically positive after 15 months. A second patient (WR-4), a 29 year-old male was considered healed after 3 months, but at the 12 month follow-up, the lesion appeared active and amastigotes of Leishmania were demonstrated in smears.

The third patient (WR-12), a 24 years-old female was considered healed at 7 months follow-up, but at 13 months there was a return of symptoms and a reactivation of the nasal lesion. The presence of parasites have not been confirmed.

Of the remaining 10 patients who received the full course of treatment, the ENT evaluation in five patients showed complete healing, after 12 to 15 months; and in five patients, after 9 to 11 months. The time of healing varied from the termination of treatment (one patient) to 6 to 11 months (9 patients).

COMMENTS:

This study designed to determine the value of intravenous sodium stibogluconate (Pentostam) in the treatment of MCL, has been concluded. During the period December 1987 to August 1989, 16 patients were studied, 9 females and 7 males.

These patients came from widely separated regions representing most of the endemic areas of leishmaniasis in the Republic of Panama.

It is of interest to note that in this group of MCL patients, the female outnumbered the males, in contrast to the cutaneous disease, in which the males greatly outnumber the females. This difference suggests a possible risk factor. The lack of specific parenteral therapy also represents a definite risk factor due to the fact that spread of the parasites beyond the primary lesion, occurs commonly along lymphatics and less commonly by the blood stream. Therefore, the practice of application of cauterizing agents, infiltration of the lesion by antimonial compounds, and the application of heat are not adequeate. In this series, 12 of the 16 patients had no history of specific parenteral therapy.

We have demonstrated two types of MCL, one representing a long term complication of the previous cutaneous lesion and the other ocurring simultaneously with the cutaneous

disease; in the latter, either as a result of direct extension of the cutaneous lesion or as a metastasic phenomenon.

The clinical symptoms and physical findings have been discussed. The constant physical findings were the involvement of the septum and the inferior turbinate. The middle and superior turbinate were never involved.

Four isolates have been identified as Leishmania panamensis from this series of patients. Five additional isolates have been obtained from patients with MCL, not included in this study, and have been identified also as L. panamensis, indicating that this species is probably responsible for MCL in Panama.

In thirteen of the patients, Pentostam was realtively well tolerated, but in three therapy had to be terminated because of toxic reactions which included cardiac, alterations, elevation of transaminases, vomiting, arthralgias and myalgias.

Of the thirteen patients who received the complete course of therapy, three were considered treatment failures, one which never showed improvement and two in which a relapse occurred at 12 and 13 months.

Of the ten patients that completed therapy and healed, one appeared healed at the end of treatment and has remained

healed after a 15-month follow up. The remaining 9 patients were considered healed after periods of 6 to 11 months post-treatment. Two of these, (WR-14 and 16) have not yet completed the twelve months follow-up (Table 5).

TABLE 1

LOCATION OF THE MUCOCUTANEOUS LESION

LOCATION	NUMBER	PERCENTAGE
SEPTUM	15/16	93.8
INFERIOR TURBINATE	8/16	50.0
MUCOSA	3/16	18.8
VESTIBULE	2/16	12.5

TABLE 2

DESCRIPTION OF THE MUCOCUTANEOUS LESIONS

TYPE	NUMBER	PERCENTAGE
GRANULOMATOUS	10/16	62.5
CRUST	5/16	31.3
INFLAMATION	5/16	31.3
ULCER	5/16	31.3
ATROPHY	2/16	12.5
SCAR	1/16	6.3
PERFORATION	1/16	6.3

TABLE 3

PRESENTING SYMPTOMS OF MCL

SYMPTOMS	NUMBER	PERCENTAGE
Nasal obstruction	16/16	100.0
Rhinorrhea	7/16	43.8
Epistaxis	7/16	43.8
Itching	6/16	37.5
Pain	4/16	25.0
Bleeding	3/16	18.8
Soreness	1/16	6.3

TABLE 4

ADVERSE REACTIONS TO PENTOSTAM

SYMPTOMS	NUMBER	PERCENTAGE
ARTHRALGIA	10/16	62.5%
MYALGIA	9/16	56.3
LIVER ENZYME INCREASE	7/16	43.8
EKG CHANGES	7/16	43.8
HEADACHE	5/16	31.3
LEUKOPENIA	5/16	31.3
NEUTROPENIA	5/16	31.3
NAUSEA	2/16	12.5
FEVER	2/16	12.5
ABDOMINAL PAIN	1/16	6.3
DIARRHEA	1/16	6.3
ANOREXIA	1/16	6.3
BRADYCARDIA	1/16	6.3

PATIENTS INCLUDED IN THE STUDY

Number	Name	Sex	Age
WR-1	A[redacted] P[redacted]	F	53
WR-2	P[redacted] de C[redacted]	F	23
WR-3	R[redacted] G[redacted]	M	21
WR-4	F[redacted] F[redacted]	M	29
WR-5	P[redacted] P[redacted]	F	61
WR-6	C[redacted] D[redacted]	M	29
WR-7	G[redacted] B[redacted] T[redacted]	M	18
WR-8	D[redacted] E[redacted] S[redacted]	F	28
WR-9	J[redacted] S[redacted]	F	31
WR-10	E[redacted] M[redacted]	F	21
WR-11	J[redacted] del C. T[redacted]	F	32
WR-12	A[redacted] L. V[redacted]	F	24
WR-13	I[redacted] S[redacted]	M	32
WR-14	F[redacted] R[redacted]	M	33
WR-15	C[redacted] A[redacted]	F	70
WR-16	P[redacted] P[redacted]	M	24

TABLE 5

FOLLOW-UP DATA

Patient No.	Post-Rx	1	2	3	4	5	6
WP-1 [redacted]	H					I	
WP-2 [redacted]	Skin I Nasal I						
WP-3 [redacted]	Skin I Nasal I	Skin I Nasal I		Skin H Nasal I			
WP-4 [redacted]	I	I		H			H
WP-5 [redacted]	I	I				I	
WP-6 [redacted]	I	I			I		H
WP-7 [redacted]	I	I		I			
WP-8 [redacted]	I	I		I			I
WP-9 [redacted]	Septal I Nostril I	I		I			H
WP-10 [redacted]	I	I		I			I
WP-11 [redacted]	Septal I Skin I Thigh H	P W H		R		P W H	
WP-12 [redacted]	I		I		I		
WP-13 [redacted]	I	I					
WP-14 [redacted]	I	I		I			I
WP-15 [redacted]	I	I				I	
WP-16 [redacted]	Skin I Mucosal I			Skin I Mucosal I			

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LE 5

UP DATA

5	6	7	8	9	10	11	12	13	14	15	17
I				H			H			H	
			Skin I Nasal W			Skin I Mucousa W	Skin H Mucousa W	Skin H Mucousa W	Skin H Mucousa W		Skin H Mucousa W
						Skin H Nasal H					
	H						W		W		
I		I			H		H				
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3/13